

Reporting of Tumor Marker Studies

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February 23, 2008

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Current State of Tumor Markers

"There are few tumor markers that are clinically useful in predicting therapeutic response or patient outcomes despite nearly 20 years of advances in molecular biology."

Hammond and Taube, *Seminars in Oncology*, 2002

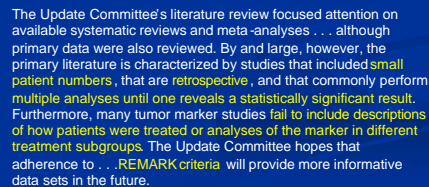
Hammond and Taube, *Seminars in Oncology*, 2002



Tumor Marker Study Deficiencies

- Unclear objectives
- Poor design
 - Poorly defined or unrepresentative cohort
 - Biased case selection
 - Design inappropriate for question/claims
 - Underpowered
- Unknown assay technical performance
- Unknown specimen quality
- Analysis problems
 - Multiple testing – multiple markers, patient subsets, endpoints, etc.
 - Cutpoint optimization
 - Model overfitting
- Poor reporting
- Publication bias

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- The image shows the front cover of a journal. At the top, it says "JOURNAL OF CLINICAL ONCOLOGY". Below that, in a dark blue box, are the words "SPECIAL ARTICLES". The main title of the issue is "American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer". Below the title, there is a list of authors: "Lynette Kuerst, Barbara Trishitt, John Sparano, Lynn Kornblith, David Slamon, Charles Hudis, Joseph Sparano, Susan A. Gelber, and Jeffrey A. Sparano".
- JOURNAL OF CLINICAL ONCOLOGY
- SPECIAL ARTICLES
- American Society of Clinical Oncology 2007 Update of
Recommendations for the Use of Tumor Markers in
Breast Cancer
- Lynette Kuerst, Barbara Trishitt, John Sparano, Lynn Kornblith, David Slamon, Charles Hudis,
Joseph Sparano, Susan A. Gelber, and Jeffrey A. Sparano
- The Update Committee's literature review focused attention on available systematic reviews and meta-analyses . . . although primary data were also reviewed. By and large, however, the primary literature is characterized by studies that included **small patient numbers**, that are **retrospective**, and that commonly perform multiple analyses until one reveals a statistically significant result. Furthermore, many tumor marker studies fail to include descriptions of how patients were treated or analyses of the marker in different treatment subgroups. The Update Committee hopes that adherence to **REMARK criteria** will provide more informative data sets in the future.



REMARK

REporting recommendations for tumor **MARK**er prognostic studies

Lisa M. McShane , Douglas G. Altman , Willi Sauerbrei , Sheila E. Taube , Massimo Gion , Gary M. Clark for the Statistics Subcommittee of the NCFEORTC Working Group on Cancer Diagnostics

- Published simultaneously in 5 journals (2005): BJC, EJC, JCO, JNCI, NCPO
- Re-reported with permission (2006): BCRT, Exp Oncol
- Endorsed by PACCT

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Goals of REMARK

- Recommend elements and formats for presentation to facilitate
 - Evaluation of **appropriateness** of study design, methods, and analysis
 - Evaluation of **quality** of study design, methods, and analysis
 - **Comparisons** across studies, including formal meta-analyses
- Ultimately improve study quality?

Target Studies

- Studies relating marker values to clinical events
 - Initially single prognostic marker, but largely relevant to predictive markers and > 1 marker
- Many points also relevant to exploratory studies not examining clinical outcome
 - Patient characteristics
 - Specimen characteristics
 - Assay methods
- Not geared to studies *developing* multiplex classifiers/risk scores, but applicable to studies *assessing* them

Introduction

1. State the marker examined, the study objectives, and any pre-specified hypotheses.

Materials and Methods

Patients

2. Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.
3. Describe treatments received and how chosen (e.g., randomized or rule-based).

Materials and Methods

Specimen characteristics

4. Describe type of biological material used (including control samples) and methods of preservation and storage.

Materials and Methods

Assay methods

5. Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.

Study design

6. State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.

Study design

7. Precisely define all clinical endpoints examined.
8. List all candidate variables initially examined or considered for inclusion in models.
9. Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.

Statistical analysis methods

10. Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.
11. Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.

Results

Data

12. Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.

Results

Data

13. Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.

Analysis and presentation

14. Show the relation of the marker to standard prognostic variables.
15. Present univariate analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.

Analysis and presentation

16. For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.

Analysis and presentation

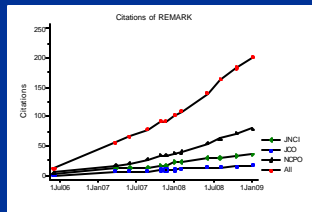
17. Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.
18. If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.

Discussion

19. Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.
20. Discuss implications for future research and clinical value.

Awareness of REMARK

- Mentioned in instructions to authors and/or reviewers: JCO, BCRT, CCR
- Citations



(Graph courtesy of Doug Altman)

Future Plans

- Nearing completion of companion explanatory document – elaboration and examples
- Formal assessment of impact – before vs. after assessment of reporting quality

Acknowledgements

- Doug Altman
- Sue Mallett
- Sheila Taube
- Other REMARK Co-authors and Supporters